

## CLAIMS:

1. The use of IL-2 common gamma chain (c $\gamma$ c) or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for  
5 modulating the interaction between c $\gamma$ c and NIK.
2. The use according to claim 1, wherein the fragment of c $\gamma$ c comprises 41MDD (SEQ ID NO:2).
3. The use according to claim 1, wherein the fragment of NIK c $\gamma$ c comprises 44MPD (SEQ ID NO:17).
- 10 4. The use according to claim 1, wherein the fragment comprises the intracellular domain of c $\gamma$ c (ICDc $\gamma$ c) (SEQ ID NO:1).
5. The use according to claim 1, wherein the c $\gamma$ c fragment comprises residues 1-357 (SEQ ID NO:20) of c $\gamma$ c.
6. The use according to claim 1, wherein the c $\gamma$ c fragment comprises residues 1-  
15 341 (SEQ ID NO:21) of c $\gamma$ c.
7. The use of a DNA encoding c $\gamma$ c or a mutein, variant, fusion protein, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain (c $\gamma$ c) and NIK.
8. The use of an antibody specific to c $\gamma$ c or to a mutein, variant, fusion protein,  
20 functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain (c $\gamma$ c) and NIK.
9. The use of a small molecule capable of modulating the interaction between IL-2 common gamma chain (c $\gamma$ c) and NIK for modulating NIK activity, wherein said molecule is obtainable by screening products of combinatorial chemistry in a  
25 luciferase system.
10. The use of a DNA encoding the antisense of c $\gamma$ c or a mutein, variant, fusion protein, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain (c $\gamma$ c) and NIK.

11. The use of *cyc* or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for treatment of a disease, wherein NIK activity is involved in the pathogenesis of the disease.
- 5 12. The use according to claim 11, wherein the fragment of *cyc* comprises 41MDD(SEQ ID NO:2).
13. The use according to claim 11, wherein the fragment of *cyc* comprises 44MPD(SEQ ID NO:17).
- 10 14. The use according to claim 11, wherein the fragment of *cyc* comprises ICD*cyc* (SEQ ID NO:1).
- 15 15. The use according to claim 11, wherein the fragment of *cyc* comprises residues 1-357 (SEQ ID NO:20) of *cyc*.
16. The use according to claim 11, wherein the fragment of *cyc* comprises residues 1-341(SEQ ID NO:21) of *cyc*.
- 15 17. The use of *cyc* or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, wherein NF- $\kappa$ B is involved in the pathogenesis of the disease.
18. The use of an antibody capable of recognizing and binding *cyc* or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment  
20 thereof, in the manufacture of a medicament for the treatment of a disease, wherein NIK is involved in the pathogenesis of the disease.
19. The use of a DNA encoding *cyc* or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, wherein NIK is involved in the  
25 pathogenesis of the disease.
20. The use of a DNA encoding the antisense of *cyc* or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, wherein NIK is involved in the pathogenesis of the disease.

21. The use of a small molecule capable of modulating NIK-c $\gamma$ c interaction in the manufacture of a medicament for the treatment of a disease, wherein NIK is involved in the pathogenesis of the disease.
- 5 22. A method for the treatment of a disease involving the activity of NIK in the pathogenesis of said disease comprising administration of a therapeutically effective amount of c $\gamma$ c or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in a subject in need.
23. The method according to claim 22, wherein the fragment of c $\gamma$ c comprises 41MDD(SEQ ID NO:2).
- 10 24. The method according to claim 22, wherein the fragment of c $\gamma$ c comprises 44MPD(SEQ ID NO:17).
25. The method according to claim 22, wherein the fragment of c $\gamma$ c comprises ICDc $\gamma$ c(SEQ ID NO:1).
- 15 26. The method according to claim 22, wherein the fragment of c $\gamma$ c comprises residues 1-357(SEQ ID NO:20) of c $\gamma$ c.
27. The method according to claim 22, wherein the fragment of c $\gamma$ c comprises residues 1-341(SEQ ID NO:21) of c $\gamma$ c.
- 20 28. A method for the treatment of a disease involving the activity of NIK in the pathogenesis of said disease comprising the administration of a therapeutically effective amount of an antibody capable of recognizing and binding c $\gamma$ c or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, to a subject in need.
- 25 29. A method for the treatment of a disease involving the activity of NIK in the pathogenesis of said disease comprising administration of a therapeutically effective amount of DNA encoding c $\gamma$ c or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, to a subject in need.

30. A method for the treatment of a disease involving the activity of NIK in the pathogenesis of said disease comprising administration therapeutically effective amount of DNA encoding the antisense of  $\gamma\gamma$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, to a subject in need.
31. A method for the treatment of a disease involving the activity of NIK in the pathogenesis of said disease, comprising administering of a therapeutically effective amount of a small molecule capable of modulating NIK- $\gamma\gamma$  interaction to a subject in need.
32. A pharmaceutical composition comprising  $\gamma\gamma$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ( $\gamma\gamma$ ) and NIK.
33. A pharmaceutical composition comprising a DNA encoding  $\gamma\gamma$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ( $\gamma\gamma$ ) and NIK.
34. A pharmaceutical composition comprising an antibody specific to  $\gamma\gamma$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ( $\gamma\gamma$ ) and NIK.
35. A pharmaceutical composition comprising a DNA encoding the antisense of  $\gamma\gamma$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ( $\gamma\gamma$ ) and NIK.
36. A pharmaceutical composition comprising  $\gamma\gamma$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein NIK activity is involved in the pathogenesis of the disease.

37. A pharmaceutical composition comprising  $\text{c}\gamma\text{c}$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein NF- $\kappa$ B activity is involved in the pathogenesis of the disease.
- 5 38. A pharmaceutical composition comprising an antibody capable of recognizing and binding  $\text{c}\gamma\text{c}$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein NIK activity is involved in the pathogenesis of the disease.
- 10 39. A pharmaceutical composition comprising a DNA encoding  $\text{c}\gamma\text{c}$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein NIK activity is involved in the pathogenesis of the disease.
- 15 40. A pharmaceutical composition comprising a DNA encoding the antisense of  $\text{c}\gamma\text{c}$  or a mutein, variant, fusion protein, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein NIK activity is involved in the pathogenesis of the disease.
41. A pharmaceutical composition comprising a small molecule capable of modulating NIK- $\text{c}\gamma\text{c}$  interaction for the treatment of a disease, wherein NIK activity is involved in the pathogenesis of the disease.
- 20 42. A method for the treatment of a disease involving the interaction between NIK and  $\text{c}\gamma\text{c}$  in the pathogenesis of said disease comprising administration of a therapeutically effective amount of  $\text{c}\gamma\text{c}$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in a subject in need.
- 25 43. A polypeptide fragment of  $\text{c}\gamma\text{c}$ , comprising the NIK binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.
44. A polypeptide fragment of  $\text{c}\gamma\text{c}$  according to claim 43, comprising 41MDD(SEQ ID NO:2).

45. A polypeptide fragment of c $\gamma$ c according to claim 43, comprising 44MPD(SEQ ID NO:17).
46. A polypeptide fragment of c $\gamma$ c according to claim 43, comprising ICDc $\gamma$ c(SEQ ID NO:1).
- 5 47. A polypeptide fragment of c $\gamma$ c according to claim 43, comprising residues 1-357(SEQ ID NO:20) of c $\gamma$ c.
48. A polypeptide fragment of c $\gamma$ c according to claim 43, comprising residues 1-341(SEQ ID NO:21) of c $\gamma$ c.
- 10 49. A DNA encoding the polypeptide fragment of c $\gamma$ c according to anyone of claims 43 to 48.
50. A vector comprising the DNA according to claim 49.
51. A cell comprising a vector according to claim 50.
52. A method for the production of a c $\gamma$ c polypeptide fragment according to anyone of claims 43 to 48, comprising culturing a cell according to claim 51 and collecting the polypeptide produced.
- 15 53. An antibody, polyclonal or monoclonal, chimeric antibody, fully humanized antibody, anti-anti-Id antibody, intrabody or fragment thereof which specifically recognises and binds a polypeptide fragment of c $\gamma$ c according to anyone of claims 43 to 48.
54. A small molecule able to inhibit NIK-c $\gamma$ c interaction obtainable by screening of molecules prepared by combinatory chemistry in a luciferase system.
- 20 55. A pharmaceutical composition comprising a polypeptide fragment of NIK according to anyone of claims 43 to 48.
56. A pharmaceutical composition comprising an antibody according to claim 53.
57. A pharmaceutical composition comprising a small molecule according to claim 54.
- 25 58. A pharmaceutical composition comprising a vector according to claim 50.
59. The pharmaceutical composition according to anyone of claims 55 to 58, for modulating NIK activity.

60. The pharmaceutical composition according to anyone of claims 55 to 58, for the treatment of a disease wherein NIK and  $c\gamma c$  interaction is involved in the pathogenesis of said disease.
- 5 61. The use of a fragment of  $c\gamma c$ , comprising the NIK binding domain or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment and/or prevention of a disease resulting from excessive immune responses.
62. The use according to claim 61 wherein the fragment of  $c\gamma c$  comprises 41MDD(SEQ ID NO:2).
- 10 63. The use according to claim 61 wherein the fragment of  $c\gamma c$  comprises 44MPD(SEQ ID NO:17).
64. The use according to claim 61 wherein the fragment of  $c\gamma c$  comprises ICD $c\gamma c$ (SEQ ID NO:1).
- 15 65. The use according to claim 61 wherein the fragment of  $c\gamma c$  comprises residues 1-357(SEQ ID NO:20) of  $c\gamma c$ .
66. The use according to claim 61 wherein the fragment of  $c\gamma c$  comprises residues 1-341(SEQ ID NO:21) of  $c\gamma c$ .
- 20 67. The use according to anyone of claims 61 to 66 , for the treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis.
68. The use of a fragment of  $c\gamma c$ , comprising the NIK binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment and/or prevention of autoimmune diseases.
- 25 69. The use according to claim 68, comprising 41MDD (SEQ ID NO:2).
70. The use according to claim 68, comprising 44MPD(SEQ ID NO:17).
71. The use according to claim 68, comprising ICD $c\gamma c$ (SEQ ID NO:1).
72. The use according to claim 68, comprising  $c\gamma c$  residues 1-357(SEQ ID NO:20) of  $c\gamma c$ .

73. The use according to claim 68, comprising  $\gamma\gamma$  residues 1-341(SEQ ID NO:21) of  $\gamma\gamma$ .
74. The use according to anyone of claims 68 to 73, wherein the disease is selected from immune thyroiditis, rheumatoid arthritis and other arthropaties, autoimmune haemolytic anemia and inflammatory bowel disease.
- 5 75. A method for the treatment and/or prevention of a disease in which activation of NF- $\kappa$ B is involved in the pathogenesis of the disease, comprising administering a therapeutically effective amount of  $\gamma\gamma$ , or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof to a subject in need.
- 10 76. A method according to claim 75 wherein the  $\gamma\gamma$  fragment comprises 41MDD(SEQ ID NO:2).
77. A method according to claim 75 wherein the  $\gamma\gamma$  fragment comprises 44MPD(SEQ ID NO:17).
78. A method according to claim 75 wherein the  $\gamma\gamma$  fragment comprises residues 1-357(SEQ ID NO:20) of  $\gamma\gamma$ .
- 15 79. A method according to claim 75 wherein the  $\gamma\gamma$  fragment comprises residues 1-341(SEQ ID NO:21) of  $\gamma\gamma$ .
- 20 80. A method of treatment and/or prevention of a disease in which NIK and  $\gamma\gamma$  interaction is involved in the pathogenesis of said disease, comprising administering to a host in need thereof a therapeutically effective amount of a polypeptide comprising a fragment of  $\gamma\gamma$ , comprising the NIK binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.
81. A method according to claim 80, comprising 41MDD(SEQ ID NO:2).
82. A method according to claim 80, comprising 44MPD(SEQ ID NO:17).
83. A method according to claim 80, comprising ICD $\gamma\gamma$ (SEQ ID NO:1).
- 25 84. A method according to claim 80 wherein the  $\gamma\gamma$  fragment comprises residues 1-357(SEQ ID NO:20) of  $\gamma\gamma$ .
85. A method according to claim 80 wherein the  $\gamma\gamma$  fragment comprises residues 1-341(SEQ ID NO:21) of  $\gamma\gamma$ .



86. A method of treatment and/or prevention of a disease in which NF- $\kappa$ B activation is involved in the pathology of the disease, comprising administering to a host in need thereof an effective amount of a small molecule according to claim 54.
87. A method according to claim 86, for the treatment of cancer.
- 5 88. A method according to claim 86, for the treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis.
89. A method of treatment and/or prevention of a disease resulting from excessive immune responses, comprising administering to a host in need thereof a therapeutically effective amount of a polypeptide comprising a fragment of  $c\gamma c$ ,  
10 corresponding to the NIK binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.
90. A method according to claim 89, comprising 41MDD(SEQ ID NO:2).
91. A method according to claim 89, comprising 44MPD(SEQ ID NO:17).
- 15 92. A method according to claim 89, comprising ICD $c\gamma c$ (SEQ ID NO:1).
93. A method according to claim 89 wherein the  $c\gamma c$  fragment comprises residues 1-357(SEQ ID NO:20) of  $c\gamma c$ .
94. A method according to claim 89 wherein the  $c\gamma c$  fragment comprises residues 1-341(SEQ ID NO:21) of  $c\gamma c$ .
- 20 95. A method according anyone of claims 89 to 94, for the treatment of diseases selected from rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, and atherosclerosis.
96. The use of  $c\gamma c$  or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulation of NF- $\kappa$ B activity.
- 25 97. The use according to claim 96, comprising 41MDD(SEQ ID NO:2).
98. The use according to claim 96, comprising 44MPD(SEQ ID NO:17).
99. The use according to claim 96, comprising ICD $c\gamma c$ (SEQ ID NO:1).

100. The use according to claim 96 wherein the c $\gamma$ c fragment comprises residues 1-357(SEQ ID NO:20) of c $\gamma$ c.

101. The use according to claim 96 wherein the c $\gamma$ c fragment comprises residues 1-341(SEQ ID NO:21) of c $\gamma$ c.

5 102. The use according to anyone of claims 96 to 101 for NF- $\kappa$ B activation.

103. The use according to anyone of claims 96 to 101 for NF- $\kappa$ B inhibition.

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